

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and for the reasons that follow.

Status of the claims

Claims 1-7 and 15 were previously deleted. Claim 14 was previously withdrawn. Claims 8-13 are pending and are represented for prosecution.

Rejections – 35 U.S.C. § 103

At the very outset Applicants thank the Examiner for acknowledging that the previous remarks in support of the patentability of claims 8-13 in view of Avital and Joon were persuasive and that the claims are not obvious in view of the combination of these references (Page 2, Paragraph 3 lines 1-2). Based on the Examiner's own admission, therefore, the claims are allegedly rendered obvious only when the teachings of Avital and Joon are combined with those of newly cited references Yasuhiko, Rajeev and Tabata. Applicants respectfully disagree.

The Examiner states that Avital teaches a diagnostic composition for detecting aspiration by instillation of charcoal particles in the trachea of hamsters, and that Avital teaches that charcoal particles may not be safe as a diagnostic tool for humans. The Examiner appears to imply that Avital specifically provides a rationale to look for an alternative to charcoal, based on what is recited in the last bridging paragraph, right column, on page 400-401. Applicants disagree. Applicants provide an excerpt from the cited paragraph:

"This hypercellularity in BAL may be explained by the fact that charcoal particles included large particles (up to 25 mm), which may remain within the lung tissue for extended periods and behave as foreign bodies, including a chronic inflammatory response. Before any attempt is made to use this method in humans, further safety studies with more animals, **smaller doses of charcoal** and **smaller or uniform charcoal particles** should be performed. (emphasis added)"

Applicants point out that the cited paragraph does not support the PTO's position that Avital provides a rationale to look for an alternative to charcoal. Avital certainly does not suggest that charcoal particles may not be safe as a diagnostic tool for humans. Instead, Avital notes a need to refine the charcoal particles utilized, and based on this exposition the skilled artisan would believe the disclosed method using charcoal particles to be appropriate as a diagnostic.

The Examiner further states on that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the charcoal particles of Avital with safe, inert, PGLA microspheres, because "the Avital et al teach charcoal particles are not safe and can be harmful to humans..." See page 6, paragraph 2 of the Office action.

Contrary to the PTO's comments in this regards, Applicants respectfully submit that Avital provides no rationale to look for a material other than charcoal, and the Examiner is using impermissible hindsight to arrive at this unfounded conclusion. Moreover, because Avital provides no indication for a desire to specifically search for a more "inert" material, as the Examiner alleges, the conclusion the Examiner draws as the rationale to combine Avital with the other cited references actually contradicts the teachings of Avital.

As stated in ¶ 2142 of the MPEP "[t]he key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." Citing the Supreme Court's decision in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007), where the Court noted that an analysis supporting a rejection under 35 U.S.C. 103 should be made explicit, the Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

Here, where the PTO has provided no principled analysis why Avital's method should be modified to use PGLA microspheres instead of charcoal the obviousness rejection is improper and must be withdrawn.

Furthermore, Applicants submit that even if the skilled artisan, regardless of the results of Avital, would have been motivated **to try** multiple different types of microspheres (which Applicant disputes, since Avital provides no such motivation), there is absolutely no guidance in Avital as to what types of microspheres would be useful in this regard. The combination of Joon, Yasuhiko, Rajeev and Tabata with Avital is arbitrary, and there is no guidance provided in any of the references alone or in combination to lead the skilled artisan to specifically select PGLA microspheres as diagnostic particles in BAL.

The only rationale the PTO provides in support of obviousness is that one would have been motivated to do so with a reasonable expectation of success since such particles are purportedly "safe, non-harmful, biodegradable and reliable". First, applicants submit that the skilled artisan would have no such motivation from Avital for the reasons outlined above. Second, even if the skilled artisan searched for a replacement for charcoal particles based on Avital's teaching, the artisan would have directed his search to finding a particle *of a smaller size* and allowing *uniform preparation* of particles suitable for BAL. Contrary to the PTO's comments, there is no reason to believe that the skilled artisan would have a reasonable expectation of success for arriving at the claimed methodology, by modifying Avital's method as suggested, because none of the references cited teach PGLA microspheres suggest their use in BAL.

Applicants remind the Examiner that previous arguments provided in this vein, namely, that it is not possible to arrive at the claimed diagnostic method based on the combined teachings of Joon and Avital were admitted by the Examiner to be persuasive.

As noted in previous responses, Joon is focused on the kinetics of biodegradation of polymeric microspheres *in vivo*. To evaluate the rate of biodegradation *in vivo*, Joon requires

a method that would simplify tracing and handling of the microspheres in living systems. More particularly, Joon teaches incorporating magnetite as a tracer for detecting microspheres in the body. See Joon at page 312, left column. Nowhere does Joon teach or suggest the use of biodegradable microspheres that are devoid of magnetite. Moreover, Joon teaches homogenization of the lung tissue to isolate and recover the polymeric microspheres prior to analyzing the extent of their degradation *in vivo*. That is, Joon's method requires animal sacrifice and would not be regarded as suitable for humans.

The newly cited references provide no guidance that would allow the skilled artisan to modify Avital's method in a manner posited by the PTO. As acknowledged by the PTO, the newly cited references inform the skilled artisan that PGLA microspheres are biodegradable and can be taken up by macrophages. There is no specific teaching in any of these references for uptake of PGLA microspheres by alveolar macrophages following aerosolized instillation, or the presence of PGLA microspheres in the lungs following intravenous administration.

Rajeev describes various properties of PLA, PGA and PGLA microspheres and emphasizes the usefulness of PGLA as a **drug carrier or drug delivery vehicle**. There is no support or foundation in Rajeev for the use of PGLA as a diagnostic tool. Tabat describes *in vitro* phagocytosis of various microparticles within peritoneal macrophages and gradual degradation of the microspheres following their uptake. Yasuhiko similarly describes different microspheres and their properties, uptake of the same within various macrophage populations, with a specific emphasis on the clearance of such microspheres from the body, and their suitability as drug delivery vehicles. None of the Yasuhiko, Rajeev and Tabata references therefore remedy the defects of Joon, noted above

The fact that PGLA microspheres are biodegradable and can be engulfed within tissue macrophages, including lung macrophages and are maintained within tissue over time does not lead the skilled artisan to their specific use in the claimed diagnostic method and, therefore, the PTO has failed to establish a *prima facie* case for obviousness.

Applicants again thank the Examiner for admitting that the pending claims are not obvious in view of Avital and Joon and submit that the newly cited references do not remedy the defects of the combination of Avital and Joon and therefore Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Given the positive conclusion of Applicants last interview with the Examiner and the Examiner's admission that previous arguments were persuasive, Applicants respectfully request that if any issue remain following a read of this response, then the Examiner contact Applicants representative prior to issuing a subsequent Office Action on the merits.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

By



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